

specification allegedly does not point to a specific portion of the WIPO patent from which the material was incorporated. Applicants respectfully disagree.

First, the specification does not merely refer to WO 95/18856, as was true in *In re de Seversky*, cited in the Office Action. Indeed, WO 95/18856 is *expressly* incorporated by reference in the specification as filed. But the specification goes farther yet. The specification states, specifically, that "[t]he invention further includes hedgehog compounds described in 95/18856 and here incorporated by reference, including homologs of hedgehog proteins, recombinant hedgehog proteins, ... [and] combinatorial mutants of hedgehog proteins as agonists or antagonists.... These and other compounds may be selected for modulating hematopoiesis and vascular growth according to the assays of the invention." Although Applicants assert that this statement is sufficient to incorporate the *entirety* of WO 95/18856 into the specification, the specification *also* points to a specific portion of the prior application, that related to the hedgehog compounds such as those recited thereafter, even if this portion is defined by subject matter rather than by line and column numbers.

Applicants respectfully direct the Examiner's attention to *Telemac Cellular v. Topp Telecom*, 247 F.3d 1316, 1329, 58 U.S.P.Q.2d 1545 (Fed. Cir. 2001), which states, "[w]hen a document is 'incorporated by reference' into a host document, such as a patent, the referenced document becomes effectively part of the host document as if it were explicitly contained therein. *Advanced Display Sys. v. Kent State*, 212 F.3d 1272, 1282, 54 USPQ2d 1673, 1679 (Fed. Cir. 2000)." Of particular note is that the entire document is considered to be incorporated – not merely a portion. By the Office Action's logic, such an incorporation would be an impossibility, because an entire document could not be incorporated by reference if it were required that "specific portions" be pointed out. Neither of the above cited cases is an aberration. "As the expression itself implies, the purpose of 'incorporation by reference' is to make one document become a part of another document by referring to the former in the latter in such a manner that it is apparent that the cited document is part of the referencing document as if it were fully set out therein." *Application of Lund*, 376 F.2d 982, 989 (C.C.P.A. 1967).

The Office Action cites and quotes MPEP 608.01(p) as exemplifying PTO policy and requirements for incorporation by reference. Although the MPEP is a fine and helpful reference,

it is not the law. In fact, the very section cited by the Examiner was discussed at length in *Application of Hawkins* 486 F.2d 569 (C.C.P.A. 1973). "After reviewing the cases on the subject and the practicalities of the situation, the court concluded that the practice did indeed have longstanding basis in the law, and that necessarily the Commissioner of Patents is vested with wide discretion to formulate rules and guidelines governing its use, thereby to prevent its abuse.... However, in the present case, we find that the addition to the disclosure of the textual material originally incorporated by reference cured any defects it might have originally had as filed, and that the application is in compliance with section 112 of the statute." *Hawkins*, 486 F.2d at 573.

It is well settled that "the standard of one reasonably skilled in the art should be used to determine whether the host document describes the material to be incorporated by reference with sufficient particularity." *Advanced Display Systems*, 212 F.3d at 1283. Applicants respectfully submit, however, that they have been unable to identify any situation in which an incorporation was found unsuccessful due to insufficient particularity. Other cases, should the Examiner choose to review them, reach a similar result. *Rolls Royce v. United States*, 339 F.2d 654, 168 Ct.Cl. 367 (1964); *Technograph Printed Circuits v. Bendix Aviation*, D.C., 218 F.Supp. 1, 31, aff'd 327 F.2d 497 (4 Cir., 1964); *B. F. Goodrich v. U.S. Rubber*, D.C., 147 F.Supp. 40, 58, [FN11] aff'd 244 F.2d 468 (4 Cir., 1957).

Indeed, courts of appeals feel strongly about this issue: "Filing cabinets abhor redundancy. Warehouses covet their space. The overcrowded conditions of offices in this city are in direct ratio to the space needed for storing of documents. The Patent Office was conceived by a document and has been prolific in that regard from its inception. These considerations warrant an economizing of words so as to alleviate these serious conditions. We do not feel that this economy will be at the expense of clarity and thereby frustrate the effectiveness of the statute." *General Elec. Co. v. Brenner*, 407 F.2d 1258, 1263 (D.C. Cir. 1968).

In summary, Applicants submit that there is no legal basis for the Office Action's assertion that only a portion of a public document can be incorporated by reference, and that any such portion must be explicitly pointed out. Furthermore, even if such a requirement were in fact applicable, the specification as filed is more than sufficient to permit one reasonably skilled in

the art to identify the portions of WO 95/18856 that Applicants have incorporated into the present specification by amendment. This conclusion is underscored by the apparent lack of any case law indicating that the words "incorporated by reference" are not themselves sufficient to effect the legal incorporation. Reconsideration and withdrawal are respectfully requested.

Specification

For the reasons set forth above, Applicant submit that no new matter has been introduced into the disclosure. Applicants accordingly have not complied with the Office Action's request to cancel the added matter.

Claim Objections

Claim 74 is objected to as allegedly failing to further limit the subject matter of the claim upon which it depends. Applicants are unable to determine the basis of this rejection. Claim 74, added in the Response filed February 22, 2000, depended from claim 72 and recited particular modes of delivery of the compound. These claims have since been renumbered as claims 72 and 70, respectively. Claim 76 was added at that time and was cancelled in the Response filed August 23, 2001, the result being that no claim 74 is presently pending. To the extent this rejection is intended as a rejection of claim 72, Applicant are unable to ascertain any colorable basis for the assertion that this claim fails to further limit the subject matter of claim 70. Clarification is respectfully requested.

Applicants further take this opportunity to point out that the Office Action repeatedly rejects claims 74 and 75, which are no longer pending. The Examiner is urged to review the response filed on August 23, 2001, in which claims 76-81 as originally numbered were cancelled, and the remaining claims numbered 67 and above were renumbered as claims 65 and above. Correction of any errors by the Office in the execution of this cancellation is respectfully requested.

Claim Rejections – 35 U.S.C. §112, First Paragraph

Claims 57-75 and 82-113 are rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to

reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Applicants respectfully traverse this rejection, as it is based entirely on an improper application of incorporation-by-reference doctrine. Reconsideration and withdrawal of this rejection are respectfully requested.

Claims Rejections – 35 U.S.C. § 112

Claims 57-75 and 82-113 are rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Applicants respectfully traverse this rejection to the extent it is maintained over the claims as amended.

Claim 83 is rejected for not defining the type of cell contacted by the compound. Claim 83 is directed to a method of stimulating hematopoiesis in an animal comprising administering a hedgehog compound having the recited structure. The Office Action acknowledges that mesodermally derived cells are susceptible to hematopoiesis induced by contact with hedgehog polypeptides. The Office Action even acknowledges that “[t]he breadth of the claims ... is *not* great” (emphasis in original) in light of the knowledge in the art and the guidance of the specification. The Office Action makes no assertion that any animal would not contain hematopoietic stem cells or undifferentiated mesodermally derived cells. Applicants submit that any such animals are so few as to constitute an insignificant number of inoperative embodiments, even if no other type of cell would undergo hematopoiesis when treated with a hedgehog compound. Accordingly, Applicants submit that the Office Action fails to establish any reasonable factual basis for asserting that one of skill in the art would be unable to practice the method of claim 83 throughout its scope without undue experimentation.

The Office Action further states that hedgehog compounds are too broadly defined to be enabled throughout their scope. First, the Office Action apparently fails to consider the limitations in the pending claims relating the structure of the hedgehog compounds to known polypeptide sequences. Accordingly, a rejection based on a broad definition of hedgehog compound as it appears in the specification without the limitations present in the pending claims is irrelevant to the enablement of such claims. The Office Action further asserts that at the time

the instant invention was filed, little was known about which parts of a hedgehog protein were responsible for activity, and asserts that across mammalian Shh proteins there is about 85% cross-species identity, while acknowledging that Shh, Ihh, and Dhh would be expected to function in the disclosed methods. Applicants direct the Examiner's attention to Chang et al., already made of record, which indicates that Hhgl-1, a mouse Sonic hedgehog gene, functions in *Drosophila* in a manner similar to the native *Drosophila* hedgehog protein, despite the fact that these polypeptides are only approximately 46% identical. Applicants also submit herewith as Exhibit A a copy of Dyer et al., *Development* 2001, 128, 1717-1730, in which a number of experiments relating to hematopoiesis were performed in mice using human hedgehog proteins. Even if it is true that mammalian Sonic hedgehog proteins share only about 85% cross-species identity, the identity is lower among mammalian Sonic, Indian, and Desert hedgehog proteins taken together, and the functional interchangeability of *Drosophila*, mouse, and human hedgehog proteins suggest that one of skill in the art would expect many *non*-mammalian hedgehog polypeptides to functionally replace mammalian hedgehog polypeptides in the presently claimed methods. Furthermore, WO 95/18856, incorporated by reference into the present application, published well prior to the filing date of the present application, and included as reference AA in the first IDS filed in the present application, contains extensive discussion of the portions of various hedgehog proteins that contribute to the biological activity of this family of signalling molecules.

Applicants respectfully point out that, despite the considerable weight apparently granted to the above factual assertions presented in the Office Action, not a single reference has been cited in support of their veracity. If the Examiner is relying on a reference not of record, Applicants respectfully request that such reference be made of record in order that Applicants may more directly address its teachings. If the Examiner is relying on personal knowledge, Applicants respectfully request that the Examiner provide an affidavit pursuant to 37 C.F.R. 1.104(d)(2).

The Office Action discusses the role of VEGF in hematopoiesis, apparently asserting that because mouse embryos deficient in flk-1 have severely reduced hematopoiesis and vasculogenesis, and VEGF itself apparently induces vasculogenesis but not hematopoiesis, the pending claims lack enablement. Applicants are unable to make any such logical leap. The

Examiner has shown no biological relationship between the VEGF signalling pathway and the hedgehog signalling pathway. Most importantly, even though *VEGF* may not have been shown to induce hematopoiesis, Applicants have shown that *hedgehog* polypeptides do induce hematopoiesis. Furthermore, the usefulness of VEGF itself appears entirely irrelevant to the enablement of variant sequences of hedgehog polypeptides which the Office Action acknowledges are useful in the presently claimed methods. Applicants respectfully request that the reasoning by which the state of the art of VEGF in hematopoiesis relates to the enablement of the presently claimed subject matter be explicitly set forth on the record.

The Office Action further argues that Applicants have not provided sufficient guidance to make a commensurate number of functionally equivalent compounds. Applicants respectfully disagree. WO 95/18856, referenced by and incorporated into the present application, discusses in great detail techniques for making and testing variant sequences. For example, WO 95/18856 discusses combinatorial mutagenesis at great length, and such techniques were highly developed in the art by the time the present application was filed. Moreover, the present application provides an assay, described on pages 40-43, which can be employed for testing the activity of such variants for inducing hematopoiesis, in addition to the other assays described in WO 95/18856 and other literature references. The mere fact that the claims recite a broad range of compounds is not itself sufficient basis to conclude that undue experimentation would be required to ascertain which sequences would be effective. The art of record clearly indicates that significant variability can be tolerated, and thus one of skill in the art, guided by the level of knowledge in the art and the disclosure of the present application and references cited therein, would have no trouble practicing the presently claimed methods throughout their scope using only routine experimentation.

The Office Action rejects claim 75, which, as has been asserted above, is not pending. If the rejection is intended to apply to pending claim 73, formerly claim 75, the Examiner is requested to refer to the claims by the corrected numbers, rather than by the numbers as filed. Even if the rejection is intended to apply to claim 73, this claim does not employ the term "synergistic effect," and therefore the definition of this term in the specification is irrelevant. The Office Action, though acknowledging that the claim has been amended, concludes that this argument is not persuasive without providing any reasoning in support of this conclusion. MPEP

707.07(f) states that "the examiner should, if he or she repeats the rejection, take note of the applicant's argument and answer the substance of it." Clarification in compliance with this section, or reconsideration and withdrawal of this rejection are respectfully requested.

In summary, Applicants submit that the bulk of the evidence available in the literature both before the filing of the present application and thereafter supports the enablement of the pending claims, and that the references cited by the Examiner fail to apply to, no less to undermine, the enablement of the pending claims. Reconsideration and withdrawal of this rejection are respectfully requested.

Claim Rejections – 35 U.S.C. § 112, Second Paragraph

Claims 57, 73, 82, 83, 85, 88, 95, 96, and 99 are rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite. Applicants respectfully traverse this rejection to the extent it is maintained over the claims as amended.

Claims 73, 82, 85, and 99 are allegedly indefinite due to the use of the term TGF- β compound. Although Applicants submit that the metes and bounds of this term would be understood by one of skill in the art, Applicants have amended this term to recite "TGF- β polypeptide." Applicants submit that this term would also be understood by one of skill in the art, as such proteins were well known in the art at the time of filing. Reconsideration and withdrawal of this rejection are respectfully requested.

Claims 57, 83, 88, 95, and 96 have been amended as suggested by the Examiner to recite an "effective amount" of the hedgehog compound. Applicants submit that this was unnecessary, because the preamble of these claims would have required an amount of a hedgehog compound effective to achieve the stated result, and that the scope of these claims is therefore not narrowed by this amendment. Reconsideration and withdrawal of this rejection are respectfully requested.

"Prior Art"

The Office Action cites Detmer et al. as pertinent to the present application. Applicants respectfully point out that a) because this reference was published long after the filing of the present application, it is not "prior art" against the present application by any definition of that

term, and b) the mere fact that there is some amount of "unknown information in the complex pathway by which hh causes erythroid cell differentiation" is irrelevant to the enablement of the pending claims. Applicants are not required to explain or understand *why* the invention works.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants submit that the pending claims are in condition for allowance. Early and favorable reconsideration is respectfully solicited. The Examiner may address any questions raised by this submission to the undersigned at 617-951-7000. Should an extension of time be required, Applicants hereby petition for same and request that the extension fee and any other fee required for timely consideration of this submission be charged to **Deposit Account No. 18-1945**.

Respectfully Submitted,

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